

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

ZHENG ET AL.

CASE NO: CL2221 US NA

SERIAL NO: 10/716,346

GROUP ART UNIT: 1634

FILED: NOVEMBER 18, 2003

EXAMINER: B. FORMAN

FOR: DISPERSION OF CARBON
NANOTUBES BY NUCLEIC ACIDS

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Ming Zheng, declare that:

I am a citizen of the United States of America and reside at 417 Harrison Drive, Hockessin, DE 19707.

I am a Research Associate at E.I. du Pont de Nemours and Company ("DuPont"), where I have worked since 2000.

I received a B.S. in Electronics from Peking University, an M.S. in Physics from University of Utah, and a Ph.D. in Chemistry from Princeton University.

I am a co-inventor of the above-identified patent application.

The following are my remarks:

1. The claims in this application have been rejected in an Office Action dated April 24, 2008 ("this Office Action").
2. I am familiar with the contents of this Office Action and understand that this declaration is being submitted in response to this Office Action to address the obviousness rejections.
3. I attach herewith as Exhibit 1 my laboratory's paper published in Nature Materials, which describes the research covered by claims 21-24 and 27 of the above-identified patent application. With an ISI Impact Factor of 19.194, Nature

Materials is considered one of the top journals, if not the top journal, in the field of materials science. Indeed, with such a high Impact Factor, the journal is one of the most important across all related physical sciences. Thus, the acceptance and publication of our work in this journal are indications of the importance and how cutting edge our research was.

4. Indeed, during the two-year period from July 2005 – July 2007, in the materials science field, our Nature Materials paper was the second most cited paper in the entire field, with 66 other journal articles citing this one paper. The report of this accomplishment is also attached herewith as Exhibit 2.

5. Our research also received extensive coverage in the scientific press. As evidence thereof, I attach herewith as Exhibit 3 an article from New Scientist where I was interviewed about our research. In that article, the author notes the surprise that my colleagues and I had when we discovered the strong interaction between DNA and carbon nanotubes (see the 5th paragraph). Also noted are our conclusions that DNA is “the most efficient way to stop nanotubes from clumping” and that DNA “provides a way to separate out nanotubes with different properties” (see the 6th and 7th paragraphs) thus solving two significant problems in the carbon nanotube field: difficulty in separating clumped nanotubes from each other (see the 3rd paragraph) and the problem of “sticky” nanotubes (see the 1st paragraph).

6. Exhibit 4 is a description of research by an NIST (National Institute of Standards and Technology) laboratory based upon “use [of] single-stranded DNA (ssDNA) to disperse the CNTs as pioneered by Zheng and coworkers at Dupont” (Abstract).

7. Exhibit 5 is a Physorg.com report detailing DuPont’s \$1.25 million grant from the National Science Foundation in collaboration with Lehigh University and MIT. The basis of this collaboration is the extension of the research in the Nature Materials paper that was eventually published in Science. As noted in the fourth paragraph of the Physorg.com report, this work was cited by Forbes magazine “as one of the top five nanotechnology breakthroughs of 2003.”

8. Other press reports are available upon request.

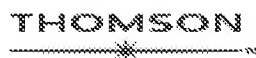
9. I declare that all statements made herein are either based on my own knowledge and are true, or if based on information and belief are believed to be

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true. I also declare that all statements were made with knowledge that willful false statements, and the like, are punishable by either fine, or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and any such willful false statements may jeopardize the validity of either the patent application, or any patent issuing thereon.

By:  _____
Ming Zheng, Ph.D.

Dated: 5/30/08_____



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Materials Science

(Sorted by citations: 3 of 73)

1 Citations: 71

Title: CONTROLLED GROWTH OF TETRAPOD-BRANCHED INORGANIC NANOCRYSTALS

Authors: MANNA L; MILLIRON DJ; MEISEL A; SCHER EC; ALIVISATOS AP

Source: NAT MATER 2: (6) 382-385 JUN 2003

Addresses: Univ Calif Berkeley, Dept Chem, Berkeley, CA 94720 USA.

Univ Calif Berkeley, Lawrence Berkeley Lab, Div Mat Sci, Berkeley, CA 94720 USA.

INFM, Natl Nanotechnol Lab, I-73100 Lecce, Italy.

2 Citations: 66

Title: DNA-ASSISTED DISPERSION AND SEPARATION OF CARBON NANOTUBES

Authors: ZHENG M; JAGOTA A; SEMKE ED; DINER BA; MCLEAN RS; LUSTIG SR; RICHARDSON RE; TASSI NG

Source: NAT MATER 2: (5) 338-342 MAY 2003

Addresses: DuPont Co Inc, Cent Res & Dev, Expt Stn, Wilmington, DE 19880 USA.

3 Citations: 57

Title: FERROMAGNETISM ABOVE ROOM TEMPERATURE IN BULK AND TRANSPARENT THIN FILMS OF MN-DOPED ZNO

Authors: SHARMA P; GUPTA A; RAO KV; OWENS FJ; SHARMA R; AHUJA R; GUILLEN JMO; JOHANSSON B; GEHRING GA

Source: NAT MATER 2: (10) 673-677 OCT 2003

Addresses: Royal Inst Technol, Dept Mat Sci Tmfy MSE, SE-10044 Stockholm, Sweden.

Armament Res, Ctr Dev & Engrn, Picatinny Arsenal, NJ 07806 USA.

Arizona State Univ, Ctr Solid State Sci, Tempe, AZ 85287 USA.

Univ Uppsala, Dept Phys, Condensed Matter Theory Grp, SE-75121 Uppsala, Sweden.

Royal Inst Technol, Dept Mat Sci, SE-10044 Stockholm, Sweden.

Univ Sheffield, Dept Phys & Astron, Sheffield S3 7RH, S Yorkshire, England.

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Self-Assembly of DNA-Wrapped Carbon Nanotubes for Sensing Applications

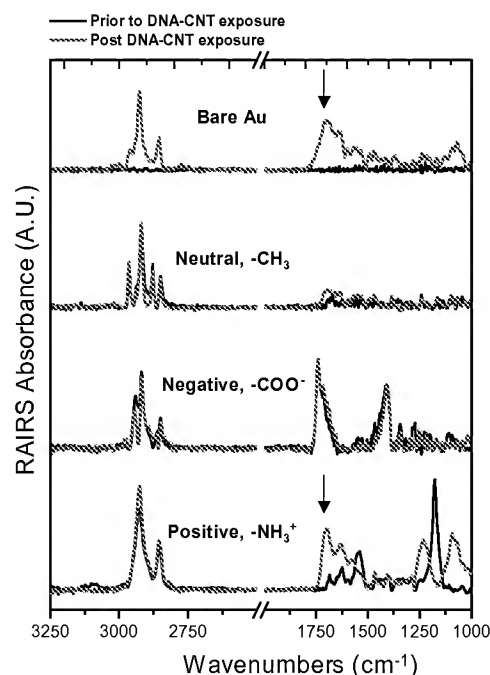
Carbon nanotubes (CNTs) are promising materials for chemical and biological sensing applications. Several studies have shown that the electrical conductivity of CNTs is extremely sensitive to changes in the local chemical environment, a property most likely resulting from the fact that all carbon atoms of CNTs reside at the surface. Some researchers have reported near single-molecule detection capabilities with CNT-derived conductivity sensors. In contrast, other groups have reported much more modest sensitivities. These discrepancies along with other irreproducible behaviors that have plagued CNT sensing studies are most likely due to the inherent polydispersity (i.e., metallic and semiconducting) of CNT samples and the difficulty in precisely assembling CNTs in sensing devices. One promising approach to these major challenges is to use single-stranded DNA (ssDNA) to disperse the CNTs as pioneered by Zheng and coworkers at Dupont. The ssDNA wraps around the CNTs and imparts a negative charge on the DNA/CNT hybrid material that allows for rudimentary purification of metallic vs. semiconducting CNTs by anion-exchange chromatography. We postulate that the ssDNA moieties will also allow for controlled placement of CNTs onto nanodevice test structures based on ssDNA-surface interactions.

R. Zangmeister, A. Opdahl, J. Maslar, and
M. Tarlov (Div. 836)

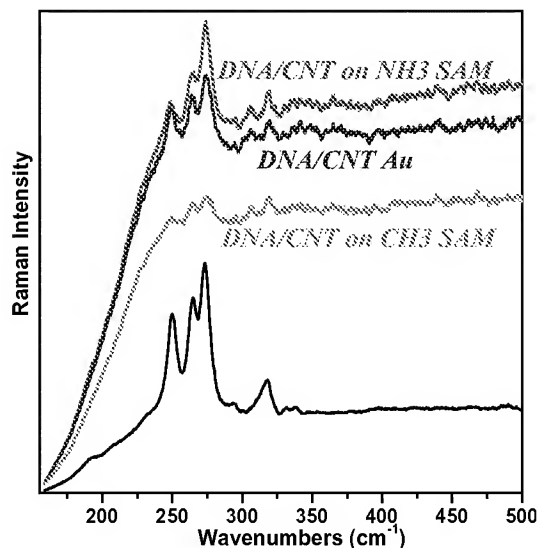
The NIST research team is studying the adsorption of DNA/CNT hybrid materials on model self-assembled monolayer (SAM) to determine which chemical functional groups can be used to anchor DNA/CNTs to surfaces. The long-term goal is to use organic monolayers to direct the placement of CNTs with nanometer resolution to fabricate conductometric-based sensing devices. Reflection absorption FT-IR (RAIRS), x-ray photoelectron spectroscopy (XPS), and Raman spectroscopy are used to study the interactions of the hybrid material with model surfaces terminated with various chemical end groups. This project is part of a larger effort within CSTL to examine this hybrid bio-nanomaterial; the separation and purification of DNA/CNT hybrid materials by capillary and temperature gradient focusing are also being investigated in CSTL's Analytical Chemistry Division.

The adsorption of the DNA/CNT hybrid materials on SAM model surfaces were examined using RAIRS, XPS, and Raman spectroscopy. The addition of characteristic DNA absorbance bands was observed on bare gold, positively charged, and on neutral (to a small extent) model surfaces as indicated by the arrows in the figure after exposure to a

solution of DNA/CNTs. The figure illustrates the DNA/CNT adsorption by RAIRS.



Raman microscopy confirmed the presence of the DNA/CNT complex on these surfaces.



The attraction between the DNA/CNT hybrid material and these surfaces was anticipated based on prior knowledge of the interactions of ssDNA on model surfaces. The negative charge associated with the ssDNA causes the

DNA/CNT material to adsorb to positively charged amine-terminated surfaces due to electrostatic interactions. Similarly, the adsorption of the hybrid material on bare gold surfaces is likely due to the strong chemisorption of DNA bases on gold surfaces. The minimal attraction of the DNA/CNT hybrid material to neutral surfaces is attributable to weaker hydrophobic interactions.

Future studies will exploit the specific adsorption of the DNA/CNT materials in conjunction with chemically patterned model surfaces to gain control over the deposition of these materials on patterned surfaces with micrometer- and nanometer-scale lateral resolution.

These studies indicate that organic monolayers can be used to selectively deposit DNA-wrapped CNTs on surfaces. The ssDNA of the DNA/CNT hybrid appears to be in a chemical environment similar to that of free DNA such that it can adsorb predictably to model SAM surfaces.

The CNT-DNA wrap: A hefty hybrid for carbon nanotubes

Since their discovery in 1991, carbon nanotubes (CNTs) have captured the public imagination. These scrolls of graphite are much too tiny to be seen but they are stronger than diamonds. Formed from organic material, they can be shaped in a variety of ways and can act as metals or as semiconductors. They offer great potential in nanoelectronics, medicine, sensing and lasers, and as strengthening elements in composite materials.

Several obstacles must be overcome, however, before CNTs live up to their expectations. Chief among these is the tendency of CNTs to clump together like strands of angel-hair pasta. Other challenges include a better understanding of CNT structures, and more effective ways of processing the tubes, sorting them, placing them on substrates, and engineering their properties.

Lehigh University, in collaboration with DuPont and MIT, recently received a four-year, \$1.25-million grant from the National Science Foundation to solve these problems by developing and studying new methods of manipulating CNTs in solution.

The Lehigh researchers will work with MIT, Cornell and DuPont through NSF's Nanoscale Interdisciplinary Research Team (NIRT) program and its Grant Opportunities for Academic Liaison with Industry (GOALI) initiative. Much of the team's focus will be on the use of single-walled CNTs wrapped with single-stranded DNA, a process that forms a helix around the nanotubes. The DNA-CNT hybrid has proven effective in CNT dispersion and researchers hope it will also aid in sorting and placing the tubes.

Several years ago, a DuPont-led research team found that DNA strands could be used to separate CNTs according to their electronic characteristics. The discovery was reported in an article in *Science* and cited later by *Forbes* magazine as one of the top five nanotechnology breakthroughs of 2003.

Principal investigators on the NIRT team include DuPont scientist Ming Zheng, Anand Jagota, formerly of DuPont and now the director of Lehigh's bioengineering and life sciences program, Slava Rotkin of Lehigh's physics department, Christopher Kiely of the Center for Advanced Materials and Nanotechnology at Lehigh, and Yet-Ming Chiang of the materials science and engineering department at MIT.

The two main goals of the NIRT team are to place CNTs on a substrate in specific locations and with specific densities and orientations, and to sort a heterogeneous sample of CNTs into constituent types.

To accomplish this, says Jagota, the NIRT team will seek to predict the structure of the DNA-CNT hybrid, given the DNA sequence and the CNT type, and to design experiments to control the placement and separation of the CNTs.

To gain greater control over the placing of CNTs on substrates, the researchers will apply a recently discovered technique called quasi-2D liquid crystal formation at a liquid-solid interface.

"If we can do what we're hoping to do," says Jagota, who is also a professor of chemical engineering at Lehigh, "we will have achieved a major advancement in CNT research."

Characterization for the NIRT project will be supervised by Kiely, professor of materials science and engineering and director of the Lehigh CAMN's Nanocharacterization Laboratory. The theoretical work will be overseen by Rotkin, assistant professor of physics at Lehigh. Both are co-PIs in the project.

Rotkin is seeking to determine whether and to what degree the nanotube structure, specifically its bandgap

structure, is altered when the CNT is wrapped by the DNA strand. He is using quantum-field analytical and numerical quantum-mechanical calculations to examine different types of CNTs with different types of DNA wraps.

"The answer to the question – does a CNT wrapped with DNA stay the same or undergo a change in properties? – depends on the symmetry and geometry of the wrap," says Rotkin.

"In some cases, the original CNT is metallic and has no bandgap. With the addition of the DNA strand, the CNT may or may not acquire a bandgap. The resulting hybrid properties and bandgap structure depend, first of all, on the original CNT properties and, second, on how the DNA is wrapped."

Rotkin and his students have succeeded in plotting bandgap structure, and mapping the areas of varying DNA-induced electric charges, which show up in repeating patterns.

"We more or less understand the rules of nature in regards to whether or not the bandgap structure [of a DNA-wrapped CNT] changes," he says. "But there are a huge number of nanotube types, and a huge number of ways of wrapping a CNT."

Source: Lehigh University

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Nanotech Report

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Nanotech TVs: Thin Is In

Move over Hummers. High definition flat panel displays are the new status symbols—and the bigger and thinner the better. Have you seen Korean manufacturer LG's recent advertisement for its 60" plasma TV? It says, "\$15K is either a very lame yacht or a very sweet TV."

In fact the consumer market for these crisp, flat screen displays is taking off. Next year 25 million units will be sold, compared to just a few hundred thousand a few years ago. The entire market is expected to exceed \$40 billion by next year.

If you haven't purchased a sleek flat panel television yet, don't despair, new nanotech-based manufacturing techniques are going to make these sets sharper and more affordable.

LCD vs. Plasma

Today, thin flat panels essentially come in two varieties, plasma and LCD (liquid crystal display). Plasma was first in the TV market to be hung like artwork. Each plasma pixel is a bubble of gas like xenon or neon sandwiched between two pieces of glass. When electric current passes through the electrodes, the gases react and activate phosphors that emit red green or blue to form a picture. **Hitachi** [HIT], **Matsushita** [MC] and **Pioneer** [PIO] are the plasma leaders.

LCDs, on the other hand, are being championed by Sharp, LG Philips (a partnership between the two companies) and Samsung. This is the same technology found in your laptop screens. It works something like the shutters on window. Thin layers of liquid crystals and color filters of red, green or blue are also similarly sandwiched between two pieces of glass. The crystals block light until they get zapped with electric charge which changes their position allowing light to pass through. Whereas each pixel of plasma emits light, LCDs have a constant backlight shining through. They have a narrow viewing angle, so if you're not facing the screen head on, the picture

is lousy. LCD's also have a slower refresh rate which means fast action images like sporting events or action movies can blur.

Plasmas have larger and brighter screens, but less definition and last only one-third as long. And worse of all,

"burn-in." This means that watching one channel, like CNBC, for too long could leave a ghost of the logo on your screen.

Both LCD and plasma televisions are many times more expensive than similar sized televisions. But prices are falling thanks to new competition from PC makers who are attracted by the larger margins in TVs and are already steeped in the business of offering LCD flat screen monitors to their customers.

Dell [DELL], for example, offers 17" LCD TVs for \$700 with their direct sales model—around half the price of Samsung's LCD 17" (\$1,200). **Gateway** [GTW] makes plasma and LCDs and has already gained a 30% market share for plasmas in only six months, topping even **Sony** [SNE]. Recognizing this threat, Samsung—whose stock has risen roughly 45% on the Korean market this year—and Sony, whose old CRT business is hurting—recently joined forces to offer LCD displays. Competition from PC marketers is great for consumers not only from a pricing standpoint, but also because the PC crowd has a history of introducing new technologies more rapidly. Think of the changes computers have seen over the past decade compared to how little your television has changed.

The growing demand for LCD's has also been a boon to chip makers like **Applied Materials** [AMAT] and **Dow** [DOW] whose special chemical vapor deposition (CVD) machines and chemicals are respectively required by manufacturers of LCDs. Unfortunately, building a new LCD plant can cost billions and many companies are looking for new approaches like nanotubes.

Nanotubes Remake the Boob Tube

Motorola [MOT] is using nanotechnology to come up with cheaper manufacturing methods and to re-enter a market they haven't been in for over 30 years.

The best nanotech products seize on a phenomenon I call "Simplicity." It means taking complexity out of current devices and simplifying it with a new material. The big clunky electron guns in the back of normal TVs now get eliminated and instead each pixel will have its own gun: a carbon nanotube.

Motorola is targeting ultra-bright displays priced to compete with plasma and LCD using technology called NED or nano-emissive display. LCDs need back lighting and use lots of power, but nanotubes emit electrons easily and, by increasing the voltage between the tip of a nanotube and the phosphor it hits, they can be brighter. But Motorola won't be a commercial contender. They have a small group developing a patent portfolio, and, as one Motorola insider tells me, "they're laying

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in the grass waiting for someone else to commercialize." Then they'll license the process to say, plasma manufacturers, who would be able to eliminate the gas components, simplify the electronic parts, and reduce the number of manufacturing steps. This would mean cheaper products for consumers buying NED displays.

The secret of NED is Motorola's growth process. While researchers used to have to make the nanotubes and then figure out how to paste them on to glass, Motorola basically plants seeds and makes the nanotubes grow on the screen like tiny blades of grass. Motorola uses chemical vapor deposition (CVD) to grow nanotubes along with a catalyst it has kept secret. It has the patents for doing this at low temperatures and on cheap glass. The carbon nanotubes form sub-pixels, which then get wired together to form a single larger pixel. If any of the sub-pixels fail, the larger pixel will still work. And if you can get phosphors down to the size of the sub-pixel, resolution will increase by at least a factor of 10.

My friend Herb Goronkin (see *Thinking Small*, June 2003), who used to run Motorola's Physical Science Labs, noted its patents cover the growth of the nanotubes and their use in flat panel displays. "The integration of nanotubes into the display is complicated," he says. "More problems get uncovered as they move through. And the integration will be the key to succeeding in the commercial arena."

DuPont [DD] already supplies materials for plasma TVs, but it's also hedging its bet with nanotubes. It scored an exclusive license from nanotech startup Nanomix (see *Company to Watch*, March 2002) to use carbon nanotubes in field emission displays. I expect its strategy to be like Motorola's, licensing its processing know-how.

Samsung and LG Philips are also using carbon nanotubes by spreading them into a polymer matrix. But while the ones that end up in the right orientation will emit light, so does the polymer. This hurts the resolution. Canon and Toshiba have struck a joint venture as well. They plan to make something sounding suspiciously similar to Motorola's NED—calling it SED or surface-conduction electron-emitter display.

Nano-Proprietary: Flat Panel Toll Collector

Marc Eller, CEO of Nano-Proprietary [NNPP.OB] (see "Nanotech Micro Cap Roster," June 2003), recently called me after he attended a display conference in Japan. His company's most important subsidiary, Applied Nanotech, had just given a presentation. Field emission was the buzz at the conference and there isn't a player not working on this. For Eller, it's a dream come true.

Like Motorola, NNPP is trying to get patents for its own growth and integration process. Applied Nanotech head Zvi Yaniv says, "We eliminated the use of semiconductor processes that people like Samsung are using for LCDs and developed CNTs in an ink format. All the prototypes we are showing today are made by techniques similar to printing high quality lithographs. The capital investment for building these factories drops by a factor of 15-20." But even if NNPP's design doesn't work or is trumped by Motorola or DuPont, it can still win—holding the patent for nanotubes in emissive state makes this little company the toll booth everyone has to pay to get on the display highway. Eller says, "Whoever Motorola ends up licensing to would be automatic licensees for us. And as long as Samsung or Toshiba or anyone else uses nanotubes, we get a piece of the action. We're going to collect a piece of every TV sold, no matter how they're made."

Eller refers to U.S. patent #5,773,921, from German inventor Till Keesman, as the "glue that puts it all together." Says Eller, "We were hunting down the basic patent for carbon nanotubes in emissive state, and we found it. It was risky putting it through the re-issue process because it was so broad. It took three years, but USPTO didn't overturn it."

Here's where things get interesting: When Canon originally paid \$5.6 million to NNPP in 1999 to non-exclusively license most of its patents, Canon didn't license all the nanotube emission ones. This meant NNPP wouldn't see any revenue from Canon's product sales using nanotubes. But the Canon/Toshiba technology appears to use other emitters besides nanotubes covered by its earlier work, and Eller informs me that the joint venture plans to begin production in March 2004 with 500,000 displays at \$3,000

each. If NNPP can strike a standard licensing deal in the 1-2% range—and that's a big if—it would reap some \$30 million off Canon/Toshiba's possible \$1.5 billion in sales. But even if they can get production up and running next quarter, which is unlikely, NNPP wouldn't start collecting until 2005. It also stands to get 2% of sales in excess of \$100 million with another Japanese manufacturer, likely Futaba. But I'm concerned about its working capital needs and how much cash is in the bank.

Company filings for nine months ended 9/30/03 report that revenues fell 30% to \$693,000, mostly from a decrease in research contracts. With the likely need for patent enforcement, a lot is riding on being able to land and enforce licensing deals. On top of this, unless the patent agreement with German inventor Keesman is amended, NNPP has to fork over \$1 million by May of 2004 to keep the patents. Right now NNPP has less than \$5 million in cash and marketable securities.

CEO Eller says his company is burning less than \$3 million a year and has enough cash on hand to last through all 2004. Side work on sensors looking to exploit government funding may help fuel the company until royalties kick in. NNPP has formed a private consortium formed with several unnamed Taiwanese and Japanese companies expecting to have a 25" color prototype flat panel by spring 2004. Its strategy will be to get the consortium to drive the technology to the other main manufacturers.

NNPP Not Ready for the Nanosphere

At \$3.09 per share, puny NNPP has a market capitalization of \$295 million. That puts it at over 250x sales and 100x book. It doesn't get much richer than this, even if all of NNPP's revenue dreams come true. While I am a big believer in this technology, the fundamentals don't support a Nanosphere investment here. However if you can stomach the risk and want exposure to nanotechnology in flat-panel big screen TVs, you could consider owning the entire value chain: Nano-Proprietary, Motorola and Dell. ■

**Nano
in the
News**

Volkswagen Partners With Nano Materials

Volkswagen entered into a trial partnership with Israeli start-up Nano Materials, a 1.5-year old spinout of the Weizmann Institute's Nanomaterials Synthesis Group. The company develops nanomaterials for use in high friction systems such as engines, gears and transmission systems. Use of its materials significantly reduce friction in moving parts without oil or grease. Expect to see other partnerships in the future with industrial equipment, avionic, and space manufacturers.

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Bush and the Nano Pretenders

In May 2002, I wrote an article entitled "Beware of Nano Pretenders," warning of the dangerous rise in companies using the prefix "nano" to capture the hype and excitement surrounding this new technology. President Bush's December 3rd signing of the \$3.7 billion nanotechnology spending bill created a big pay day for many companies using nanotechnology mostly for its marketing advantages. To be sure, a number of our Nanosphere companies also benefited. Our top Nanosphere pick for November, NVE Corporation [NVEC], rose 25% on the month.

But then there was molecular diagnostics developer **Nanogen** [NGEN]. Nanogen skyrocketed 51% on news of U.S. patent 6,652,808—which according to the company's press release "may" help assemble "nanocomponents" into larger scale devices. The release using buzz phrases like nanofabrication, self-assembling nanostructures and nanoparticles looked like an attempt to ride the new bill's momentum, because the truth be told, Nanogen's news was no news.

Listen to the comments of nanotech IP expert Stephen Maebius of Foley & Lardner, "It is surprising that a method of manufacturing patent, traditionally considered a weaker type of patent, would turn out to be such a valuable piece of IP from an investor perspective." Still, by market close on December 3, GENE had added nearly \$50 million to its market cap.

Investors should have paid more attention to news from **DuPont** [DD] a day earlier. DuPont announced a "key nanotechnology discovery" which showed a real application using DNA to separate out different kinds of carbon nanotubes—one major problem involved in their production. Rather than use Nanogen's process, DuPont uses anion exchange chromatography. But DuPont, a larger and more capable developer, saw its stock drift lower in spite of this nanotech breakthrough.

I called Nanogen co-founder Mike Heller to ask if the company has worked with a "nanocomponent" like nanotubes. Heller said Nanogen had not yet worked with them or any other "nanocomponents." Nanogen executive vice president Dave Ludvigson said the company was inspired to issue the release in part after seeing private nanotech startup companies, like Quantum Dot Corp. and Nanosphere Inc., make similar statements.

The problem is that investors misunderstand Nanogen's patent and the company does-

n't go out of its way to set the record straight as long as this misperception helps its stock price. Nanogen was issued nine patents this year, but only issued press releases for two which had "nano" in their names.

We doubt Nanogen's well-timed press release violated any disclosure rules. However, the fact remains that Nanogen is barely in the field of nanotechnology. It makes microarrays and sells them to labs for genetic testing. That's what they do. Most of their patents are for using electric fields to move DNA around their chips. The patent which sparked the price explosion was originally filed in 1996 before things like quantum dots and nanotubes were popularly used. It now covers attaching DNA to so-called "nanocomponents" to help assemble things by using electric current on one of their microarrays. It reads broadly but basically means if you stick something to a piece of DNA and use an electric field to get that DNA to then move somewhere, you'd be using their patent. It's never been established that DNA is the best way or even a good way to do this. At best this represents some small licensing revenue many years in the future.

One unlikely beneficiary of Nanogen's patent announcement was metrology tool vendor **Nanometrics** [NANO]. As I warned in my Nano Pretenders article over a year ago, Nanometrics' NANO ticker is its only connection to nanotechnology. It makes instrumentation that measures the thickness of deposited films. Yet the stock jumped more than 10% during intraday trading on December 3rd on 4.5 times its average daily volume of 351,000 shares.

Another "nano in name only," **NanoPierce Technologies** [NPCT.OB], jumped as much as 24% on nanotech bill signing day. Stocks of smaller nanomaterials developers were big beneficiaries of the President's bill signing. **Altair Nanotechnologies** [ALTI] rose as much as 128%, while **Nanophase** [NANX] shot 61% higher during the month with no tangible news. **Harris & Harris Group** [TINY] also rose 35% on the month as investors repriced the value of their private investments given the speculative rise in nanotech stocks. TINY now trades at 4.48x its NAV of \$2.11, tracking near its all-time high multiple from the bubble years.

As one of the few nanotechnology insiders invited to President Bush's nanotech spending bill signing, I was ecstatic to find out first hand that the President shares my enthusiasm for this growing field. I also believe that nanotechnol-

The Insider

It was a historic month for nanotech and I was lucky to be on the front lines. What was the Oval Office like? Well, one interesting detail is that on the President's 19th century desk, the coat-of-arms shows the eagle looking to the arrows in his right talon, a symbol of war. But on the carpet, the eagle looks at the olive branch in his left, towards peace. Times have changed. And in technology they do so faster than ever. The telephone took 36 years to reach 25% of the population. The Internet hit critical mass in 23 years and cell phones in just 14. Now comes flat panel TVs. Nanotech will make them more affordable with better quality in the coming years.

A lot of you have been writing in asking me about my opinion on NNPP. I think that future potential is already priced in. For my reasons, please see my comments on in our cover story, "Nanotech TVs: Thin Is In" on page 2. Warmest holiday wishes to your family! E-mail me at nanotech@forbes.com. Here's to thinking big about thinking small.



ogy and companies making nanotechnology a reality with exciting breakthroughs deserve more attention from investors. This is the kind of pertinent investor information that we have been delivering to you in this newsletter since the spring of 2002. However, investing in nanotechnology stocks is not for widows and orphans and opportunistically timed press releases don't make for sound investment strategy. My team carefully analyzes the technology and fundamentals of each stock in our Nanosphere portfolio. We will continue to inform you of which stocks make the grade and which don't and above all, try to help you steer clear of the "nano-pretenders." ■

Top 5 Nanotech Breakthroughs of 2003

This year has been a monumental year for nanotechnology, from President Bush signing the historic \$3.7 billion Nanotechnology Research & Development Act to Wall Street heavyweights like Merrill and Credit Suisse inaugurating coverage. But as we noted last year (see "Top 5 Nanotech Breakthroughs of 2002," December 2002), the most exciting advancements in nanotech are still the scientific developments taking place in universities, startups and major corporations alike. Over the past month, my team at Lux Capital interviewed the world's leading researchers in quantum physics, chemistry, biology, and engineering to determine the top nanotechnology scientific breakthroughs of 2003.

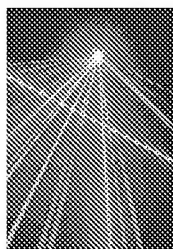
1. In Vivo Biological Labeling with Quantum Dots



Researcher(s): Quantum Dot Corp. & Albert Libchaber and Ali Brivanlou (Rockefeller University)

Researchers at Quantum Dot Corporation and Rockefeller University announced two major breakthroughs toward advancing quantum dots for use in biological imaging. First, the team at Quantum Dot simultaneously detected two cellular targets with one light source instead of the traditional two. Then researchers at Rockefeller developed procedures for using quantum dots to label live cells and demonstrated their use for long-term multi-color imaging of live cells. These approaches should permit the simultaneous study of multiple cells (such as breast cancer tumors) as they proceed through growth and development.

2. World's Smallest Lasers



Researcher(s): Charles Lieber, Xiangfeng Duan, Yu Huang & Ritesh Agarwal (Harvard University)

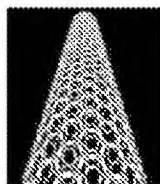
"I think the hottest nano-activity this year has been in electronics & optoelectronics," says Philip Ball,

consultant editor at *Nature*. He cited Nanosys co-founder Charlie Lieber's work on a single-nanowire electrically driven laser as one of the top breakthroughs of the year. Currently, lasers that send information-laden light pulses down fiber-optic networks are about 1,000 times bigger than these nanowires and too cumbersome to fit onto silicon chips. Previously, researchers have been able to build nanowire lasers, but only individually. Lieber showed a way to get large arrays of single-nanowires, electrically driven lasers to self-assemble. This will make light-based information technology faster and more compact.

3. Nanotube Separation Technology

Researcher(s): DuPont [DD], the University of Illinois at Urbana-Champaign and the Massachusetts Institute of Technology

According to DuPont's Ming Zheng, "The separation of carbon nanotubes is the single greatest impediment to their technological application." Zheng found that single-stranded DNA strongly interacts with carbon nanotubes. Since carbon nanotube-DNA hybrids have different electrostatic properties that depend on the nanotubes' diameter and electronic properties, they can be separated and sorted using a process called anion exchange chromatography. This finding opens the door to carbon-nanotube-based applications in biotechnology



4. World's Fastest Transistor

Researcher(s): Milton Feng, Walid Hafez and Jie-Wei Lai (University of Illinois at Urbana-Champaign)

Researchers at the University of Illinois at Urbana-Champaign broke their own record for the world's fastest transistor in 2003. Their latest device, with a frequency of 509 gigahertz, is 57 gigahertz faster than their previous record holder. Unlike traditional transistors, which are built from silicon and germanium, these are made from indium phosphide and indium gallium arsenide. "This material system is inherently faster and can support a much higher current density," says Milton

Feng, professor of Electrical and Computer Engineering at Illinois. Feng's other speed secret? He designed a transistor with a 25nm base and a 75nm collector.

5. First 3-D Assembly of Magnetic and Semiconducting Nanoparticles

Researcher(s): Columbia University & IBM [IBM]

Researchers at IBM Watson Research Center and Columbia University have created a new, three-dimensional designer material, or "metamaterial," assembled from two different types of particles only billionths of a meter across. This experiment demonstrates the ability to bring more materials together than previously realized. Its tunable magnetic properties and optical properties wavelengths in the infra-red could be important for fiber optic communications applications.

Looking Ahead to 2004

As we predicted last year, nanobiotechnology has seen significant advancements during 2003. Not only have quantum dots been embraced by the biotech community, but the leading orthopedic and dental care companies have shown quantum leaps in their technology (see "Nanohydroxyapatite: Nanotech in Your Smile," May 2003), cancer companies like Triton Biosystems (see "Nanotech Takes on Cancer," November 2003) continue to advance new nano-enabled therapeutics, and even the FDA began to embrace nanotech when it approved Starpharma's use of a dendrimer-based anti-AIDS gel. What's in store for 2004? Here are two predictions

1. Nanoinprint Lithography (NIL) will be adopted by the semiconductor industry. It's not nanobio, but NIL is just too large to ignore. NIL needs just improvements to defect densities and better alignment for widespread industry adoption. Companies like Sweden-based **Obducat** [OBDU.B] and Molecular Imprints (see *Companies to Watch*, January 2003) will benefit.

2. FDA will fast-track nano-enabled cancer treatment. Whether it's dendrimer, magnetic nanoparticle/antibody, soluble Taxol, biosilicon, or gold nanoparticles, nanotech-enabled cancer treatments are flooding the therapeutic drug pipelines. The National Cancer Institute recently made nanomedicine one of its top 5 priorities and we wouldn't be surprised to see the FDA follow suit. ■

Nano in the News

Nanosys named *Scientific American's* 2003 Business Leader in Nanotechnology
Nanosys, Inc. was named 2003 "Business Leader in Nanotechnology" on the "*Scientific American* 50." (Full disclosure: Lux Capital, through its subsidiary, Angstrom Publishing, publishes the *Forbes/Wolfe Nanotech Report*. Lux Capital is an investor in Nanosys.)

Thinking Small: Phil Kuekes

I was blown away by Phil Kuekes' talk while with him in Singapore. He's likely to lead the next paradigm shift in Moore's Law from integrated circuit to molecular electronics. Phil is the chief architect in Quantum Science Research at Hewlett-Packard Laboratories and has developed architectures for chemically assembled electronic nanocomputers for the HP-DARPA Moletronics program. He was project manager for Teramac, a trillion operations per second reconfigurable computer that was the largest defect-tolerant machine ever made. Phil holds 14 patents in molecular electronics and parallel computer architectures and received the 2000 Feynman Prize in Nanotechnology (with James R. Heath and R. Stanley Williams).

Why molecular electronics?

I'm a beneficiary of Moore's Law. I designed machines that did millions of operations per second in the 70s, billions in the 80s and now trillions in the 90s. But it became clear to me as Moore's Law continues exponentially, it nears the atomic limits. We're getting down to the molecular level of assembly. Why not jump in to it?

And what has your approach been?

The approach came first from the parallel architecture that became the HP/Intel I64 chip. We had done things very relevant to building at the molecular scale. When I talked with Stan Williams (*see Thinking Small, June 2002*), I knew it was possible to build a machine that would work with large number of defects. We were inspired by the architectural ideas we'd developed on TeraMac, a 400 pound supercomputer built out of ordinary silicon, with 75% of the chips being bad. The conventional idea of electronics is to have very few defects, yet it ran 100 times faster than a workstation. We found the defects and wired around them.

Why doesn't my computer have this design?

The area of your silicon chip would have to increase ten fold. When the cost of your house insurance is ten times the price of your mortgage you should move to another

neighborhood. The cost of creating a bit of memory plus a switch is six or seven transistors. But the area of that is roughly 20 times the area of the intersection. To detour around bad things, you need intersections around roads. In a city, the only way to do that would be with a freeway that would take up vast space. That's what you'd have to do with CMOS. But if you had molecular electronics you could form a bit plus a switch in an area incredibly small compared anything else.

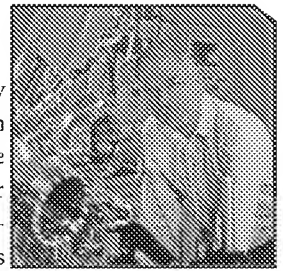
What about scaling down the normal chip making process?

We wanted something that would get better as technology scales down. As you shrink lithography, you get a countable number of atoms. The electrons behave like waves as much as they do particles and ordinary chips stops working normally. But we set up to create a switch which would only work at the scale. When you know your goal is to reach the end point to deal with individual atoms or clusters, you better choose the rules of physics that works at that scale. We have a mechanism that could turn on and turn off quantum tunneling at that scale. And what becomes a problem for existing technology as it shrinks, becomes our mechanism. We're not trying to reinvent the 1947 transistor, we're trying to reinvent the 1958 integrated circuit. Every time a chip shrinks it needs to be aligned with more mechanical precision. We're trying to replace mechanical precision with computation whose price has dropped dramatically.

You call this Non-Eli Manufacturing. Why?

Eli Whitney was a father of the industrial revolution. Like the NNI, he was working on a government project too. They needed to buy rifles which were inexpensive. He invented interchangeable parts. Previously, they didn't spend too much on casting the parts that went into the rifle, so the molds weren't good. Skilled craftsmen had to file down the parts make them fit and get the rifle to work. So you spent more on labor than physical

capital. Eli Whitney minted a fortune in capital equipment. He paid very little in labor and instead had mechanically precise parts that would all fit together.



And you're proposing to do the opposite?

To continue to make progress we have to turn the process on its head. The rising cost of chip fabrication plants is because of the mechanical precision required. So instead let's use chemical assembly processes and build a bunch of things full of defects, but now I'm going to use cheap labor (from a supercomputer) to fix them up. It's possible for machines to find out what's not working, and the cost to do it with a computer will get lower and lower. This is our technological bet, even though it's not proven just yet. What the skilled labor had to do back in Whitney's day, we let a computer do. In principle, this is a new way of thinking about a whole variety of manufacturing. The most obvious is in making computer like structures. We're making a very explicit trade-off. The price to assemble chemically would be very low. But for every device I build, I have to in real-time in the supercomputer next door, do just in time design. Thinking about this only became reasonable in the late 90s when CAD got good enough. You'll be able to measure, analyze, then come back and download the design.

Where did this inspiration come from?

I'm talking to you right now from Florida looking at palm trees outside my hotel. From you and I and the palm trees, you can grow things, you don't need a lot of assembly techniques. But it has taken 4 billion years of R&D. We're trying to do something that can be done in the next few years and have chips chemically-assemble with a little help from the supercomputer in the next room. The palm tree carries all the instructions for assembly inside the DNA. A lot of the instructions could exist in the supercomputer. In principle, you could make enough molecules to do this in one test tube to supply the entire world. If I could start to build very small computers the size of bacterium, they could be incorporated into other devices. Those devices could make the manufacturing of other things less expensive. ■

Nano in the News

Bush Signs \$3.7 Billion Nanotech Bill
President George W. Bush signed off on a 4-year, \$3.7 billion bill for nanotechnology research funding, putting the National Nanotechnology Initiative into law. The 21st Century Nanotechnology Research Act is designed to help develop breakthroughs in nanotechnology that will lead to new products, new businesses, new jobs and new industries.

Companies to Watch

QinetiQ Nanomaterials Ltd.

[Private]

www.nano.qinetiq.com

+44 (0) 1252 393000

Farnborough, U.K.

Chief Executive: Sir John Chisholm (CEO of parent QinetiQ)

What it does: Develops and supplies bulk and tailored nanomaterials.

Nanotechnology is not just a product of leading academic and corporate research labs throughout the world. Government agencies are also committing substantial amounts of money to nanotech development, especially for national defense. One such example is QinetiQ, spun off from the UK's Ministry of Defense. In 2001, the British Government's "Defence Evaluation and Research Agency" (DERA)—the British equivalent of the U.S.'s DARPA—split in two. One part handles the most sensitive areas of military research and remains under the control of the Ministry of Defense. The other part, QinetiQ Group plc, opted for a Public Private Partnership. The Washington D.C.-based private equity firm The Carlyle Group took a 34% equity stake in the company and is acting as its strategic partner. Privately held QinetiQ has more than 8,000 scientists and engineers who have been responsible for some of the 20th century's most important scientific breakthroughs, from the jet engine to liquid crystal displays.

QinetiQ Nanomaterials Ltd. (QNL) is a wholly-owned subsidiary of QinetiQ and has been active in producing nanoparticles. QNL is worth knowing about because it is the first U.K. company dedicated to bulk production of nanomaterials. And QNL will be the main supplier of nanomaterials for Europe's largest science & tech company, its parent QinetiQ, which is working on a host of nanotech applications from nano ceramics for fuel cells to nanoscale silicon devices for MEMs. QNL has an exclusive worldwide license to a nanoparticle processing technology invented by a U.K.-based company called Tectronics. It allows QNL to make nanoparticles of anywhere from 20nm-100nm and to make them with a wide variety of materials, from metals (e.g. aluminum and copper) to oxides (e.g. copper oxide and zinc oxide). Tectronics' method is also able to produce mixed, layered, or doped materials. These modified nanomaterials are very popular right now in sectors like health care and technology. BASF's [BASF] cosmetic Z-Cote uses zinc-oxide nanoparticles, while Oxonica (see *Companies to Watch*, November 2003) uses doped versions of zinc oxide nanoparticles to create a more efficient and healthier sun-screen. The ability to produce layered metals or structured oxides could lead to dramatic improvements and efficiencies for the estimated \$2.8 billion catalyst market because of these layered structures (e.g. cheaper core materials could be coated with catalytic material)

Paul Reip, managing director of QNL, says it is developing the U.K.'s first production facility dedicated to the volume production of specialty nanomaterials. QNL's revenues come from sales of nanomaterials and development contracts. Revenues are expected to increase significantly in the next year after finalizing development contracts with external partners and starting new projects with parent QinetiQ. QNL is also actively seeking new partners and customers to continue increasing its product portfolio through specialized client developments. Reip says the company anticipates an IPO for QinetiQ in the next 2-5 years, creating yet another public vehicle offering investors exposure to nanotechnology.

NanoCoolers, Inc.

[Private]

www.nanocoolers.com

(512) 327-4160

Austin, Texas

Chief Executive: Jim Moore

What it does: Develops cooling devices for computers to refrigerators.

Cooling is the name of the game at Austin, Texas-based NanoCoolers, Inc., but we're not talking about keeping beer cold for a tailgate. This is about harnessing nanotechnology to cool computers. The faster and more powerful computer processors get, the hotter they run. Many manufacturers now use something called a heat pipe—a small copper tube filled with water that cycles through boiling and condensation to draw heat from the chip. But as Moore's Law marches on, processors' temperatures will become too hot sometime in 2005.

This is where NanoCoolers comes in. They're taking the heat pipe to a new level, replacing water with liquid metal and using an electromagnetic pump that requires no moving parts. "Our solution is elegant, simple, very low power, inexpensive, and a good four orders of magnitude [of heat dissipation] better than current heat pump solutions," says CEO Jim Moore. NanoCoolers has joint development activities with two major industry players, likely IBM [IBM], Hewlett-Packard [HPQ], or Dell [DELL]. NanoCoolers expects to have its heat transport products on the market by the first quarter of 2005.

But that's not all. NanoCoolers is also aiming to replace the compressors in your home refrigerator or air conditioner with its nanotech-powered cooling devices. Here it's capitalizing on the basic principle of thermoelectrics: If you pass electrical current through a solid-state thermoelectric device, one side gets hot and the other side gets cold. Draw heat away from the hot side, and you can use the cold side to cool. Current thermoelectric technology isn't as efficient as traditional compressors, but NanoCoolers hopes to change that in late 2005 with nanostructures. These new devices should be more reliable and efficient, and will avoid the environmental problems of compressor gases such as chloro-fluoro carbons and ammonia.

NanoCoolers was founded in 2002 with the intellectual input of former IBM [IBM] scientist Uttam Ghoshal, now the CTO. It received \$4 million in startup funding from Austin Ventures LP and has just received \$11.3 million in funding from Draper Fisher Jurvetson, Austin Ventures and an unnamed corporate investor. CEO Moore estimates that the company should now have enough cash to carry them well into 2005, when they expect to start generating revenue.

NanoCoolers' main competition comes from Mountain View, California-based Cooligy. Where NanoCoolers is cooling chips through liquid metal and an electromagnetic pump, Cooligy is using a water-based fluid and osmotic pressure. Both systems avoid moving parts, but NanoCoolers' device uses less power and is orientation independent, which means it can be used in notebook computers.

Moore has been involved in three startup companies besides NanoCoolers—Crossroad Systems [CRDS], Alchemy Semiconductor (acquired by Advanced Micro Devices [AMD] in 2002) and Boxx Technologies. About NanoCoolers, Moore says that, "We're a small company, still in the startup mode and increasing our staff quickly. We hope to have a lot more good news in 2004." Watch for it. ■

Follow the Money

A monthly look at who in nanospace is getting funding and who's giving it.

State & Government Funding

Dendritic NanoTechnologies Inc./Central Michigan University

Location: Mount Pleasant, Michigan

Funding Announced: 11/18/03

Funding Amount: \$3 million

Notes: Dendritic Nanotechnologies, a subsidiary of Australia's **Starpharma** [SPLAX] (see *Companies to Watch*, December 2002), announced a \$3 million grant extension in addition to a \$3.5 million 2002 U.S. Army grant to create a Center for Dendrimer Based Nanotechnology at Central Michigan University. The funds will be used to purchase nanoscience instrumentation and equipment – this could potentially benefit Nanosphere companies **Veeco** [VECO] and **FEI Company** [FEIC]. Dendritic NanoTechnologies is one of seven charter members of the Institute for Soldier Nanotechnologies, a \$50 million project managed by Massachusetts Institute of Technology to develop nanotechnology for the Army of the future. Other charter members include **DuPont** [DD], **Raytheon** [RTN], **Dow Corning**, **Nomadics**, **Carbon Nanotechnologies** and **Triton Systems**.

Zyvx Corporation

Location: Richardson, Texas

Funding Announced: 11/12/03

Funding Amount: \$600,000 NASA SBIR Phase II

Notes: Zyvx Corporation, a developer of nanotechnology materials, tools, and structures, was awarded a two year \$600,000 NASA Small Business Innovation Research Phase II award. The program's objective is to develop ultra-high-strength, low-weight composites for aerospace applications. One major roadblock to large-scale manufacturing of products made with carbon nanotubes is their poor solubility. This program aims to develop an approach that increases carbon nanotube solubility without damaging or degrading nanotube properties. The original program was initiated in February 2003 with the Phase I award.

NanoInk, Inc.

Location: Chicago, Illinois

Funding Announced: 11/18/03

Funding Amount: \$100,000 NIH SBIR Phase I

Notes: NanoInk (see *Companies to Watch*, July 2003) received a \$100,000 Phase I grant of a potential two-part \$1.3 million Small Business Innovation Research grant from the National Institutes of Health (NIH). The grant is for development of NanoInk's Dip Pen Nanolithography (DPN) technology for scaling down bio-arrays. Using this process, NanoInk could potentially create nanoarrays that are up to 10,000 times smaller than current microarray technology. The NanoInk grant is the result of a special NIH initiative to support multidisciplinary work of nanotechnology in medical applications.

Venture Capital

Molecular Imprints, Inc.

Location: Austin, Texas

Lead Scientist/CEO: S.V. Sreenivasan/Norman Schumaker

Funding Announced: 12/2/03

Investors: Alloy Ventures, Draper Fisher Jurvetson, Motorola [MOT], Carl Zeiss SMT AG and Hakuto Co. Ltd

Funding Amount: First \$15 million close of ongoing \$30 million (Series B)

Notes: Molecular Imprints (see *Companies to Watch*, January 2003) is a nanoimprint lithography (NIL) toolmaker. NIL is a stamping lithography technique that can deliver 20nm resolution at 1/10th the cost of traditional optical lithography methods used for semiconductor manufacturing. Molecular Imprints' competitors include New Jersey's Nanonex, EV Group of Austria, and Obducat of Sweden. But with an expected \$30 million in funding on top of a previous round of \$12 million in early 2002, Molecular Imprints will be well positioned.

NPoint, Inc.

Location: Madison, Wisconsin

Lead Scientist/CEO: Max Lagally, Ph.D./John Biondi

Funding Announced: 11/24/03

Investors: Wisconsin-based Angel Investors

Funding Amount: \$600,000 (Series B)

Notes: NPoint, Inc. (see *Companies to Watch*, October 2002) makes precision instrument nanopositioning systems, a crucial control component in nanotechnology research tools such as Atomic Force Microscopes (AFMs) and Scanning Electron Microscopes (SEMs). NPoint targets the installed metrology equipment market with retrofit kits to update outdated systems. This round of funding is in addition to \$3 million in federal grants and \$1.14 million of previous funding. The fact that Veeco outsourced a major MultiMode Pico-Force component to NPoint (a first) is a testament to the NPoint's technology leadership.

Mergers and Acquisitions

Target: Advanced Imaging, Inc.

Acquirer: Veeco [VECO]

Acquisition Price: \$60 million

Acquisition Date: 11/19/03

Notes: Veeco continued its hunt for companies with complementary technologies by purchasing privately-held Advanced Imaging, Inc. of Camarillo, California. The \$60 million cash deal also included three-year earn-out payments of up to \$9 million. Advanced Imaging's key product enables precise material removal within 3 nanometers. Technology like this will allow hard drive manufacturers such as **Seagate** [STX] to move from making 80GB hard drives to those 120GB and over. Advanced Imaging had revenue of \$33 million for the 12 months ended Sept. 30.

The Nanosphere

Company (symbol)	Technology	Coverage Initiated	Current Price	52 Week Range	Market Cap (\$mil)	Buy/Hold/Sell
Intellectual Property Incumbents <i>Leading researchers in nanotech, with big potential for spin-offs and revolutionary breakthroughs.</i>						
IBM [IBM]	Nanoscale storage and nanotube transistors	3/02	\$92.40	\$73.17-\$94.54	\$158,970.00	Buy
Hewlett-Packard [HPQ]	Molecular transistors and switches	3/02	22.20	14.18-23.90	67,690.00	Buy
Instrumentation <i>Tools that allow researchers to view and manipulate nanoscale matter.</i>						
Veeco [VECO]	Atomic Force Microscopes	3/02	27.07	10.94-30.25	792.91	Buy
FEI [FEIC]	Focused Ion and Electron Beam Microscopes	1/03	21.66	13.55-28.75	717.77	Buy
Materials <i>Companies producing nanoscale materials with novel properties that have applications across a wide range of industries.</i>						
Symyx [SMMX]	Novel materials discovery	3/02	19.03	11.40-25.63	599.43	Buy
Modeling <i>Companies developing software to visualize, model and simulate matter and activity at the nanoscale.</i>						
Accelrys/Pharmacopeia [PCOP]	Molecular rendering and analysis software	3/02	12.37	5.94-16.11	294.96	Buy
Platform Technologies <i>Companies that have controlled key intellectual property that will be the foundation of future developments.</i>						
Nanosys [private]	Nanowires and nanostructure-enabled devices	3/02	n/a	n/a	n/a	n/a
NVE Corporation [NVEC]	Spintronics-based MRAM	7/03	50.50	5.00-60.33	218.16	Buy
Investment Firms <i>Companies that are investing in promising early-stage nanotechnology startups.</i>						
Harris & Harris Group [TINY]	Non-volatile RAM, drug delivery, nano-optics	5/02	9.45	2.23-10.72	108.67	Sell
Nanobiotechnology <i>Companies that are working at the intersection of nano- and bio-technology.</i>						
SkyePharma [SKYE]	Nanoparticle solubilization for drug delivery	8/02	13.57	6.22-14.35	832.64	Buy
Flamel Technologies [FLML]	Nano-encapsulation for drug delivery	8/02	24.80	3.51-43.60	404.91	Buy

Word on the Street

IBM: Big Blue researchers announced a breakthrough in molecular circuitry design, creating a system that works with existing methods of electronics manufacturing. IBM says it used a naturally occurring pattern of molecules as a stencil to etch flash memory circuitry into silicon. The holes in the pattern are about 20nm across and 40nm apart. IBM says self-assembly techniques could be used in pilot projects 3-5 years from now. We continue to believe IBM will be responsible for many of nanotech's most significant breakthroughs.

HPQ: Hewlett-Packard was lower on the month, despite beating earnings estimates. The problem? Margin erosion. HP's 25.4% gross margin fell short of most analysts' expectations and investors are concerned that HP's margins will continue to drop due to fierce competition from new rival Dell [DELL]. For its fiscal Q4, HP earned \$862 million (\$0.28 per share) on \$19.9 billion in revenue, compared to earnings of \$390 million (\$0.13 per share) on \$18.05 billion in revenue a year ago. CEO Carly Fiorina blessed Street estimates for profit of \$1.43 a share on revenue of \$77.6 billion for 2004 and forecast 20% profit growth next year and beyond, citing an improv-

ing economy and solid consumer demand.

VECO: The Veeco deal machine continued to steam ahead (See *Follow the Money*, p. 7), as the company acquired Advanced Imaging Inc., a privately held data storage equipment vendor for \$60 million cash and three-year earn-out payments of up to \$9 million. Last month, Veeco agreed to buy Emcore's [EMKR] semiconductor test equipment for \$60 million cash.

FEIC: FEIC shares have been weak because of declining margins and concerns of a bloated cost structure. FEIC has been excluded from the semiconductor rally over the past few months, and we think FEIC looks attractive at current levels.

SMMX: Symyx has drifted lower on a lack of news and new development deals. Its upcoming Q4 should be strong, as its broad development deal with ExxonMobil [XOM] (44% of Q3 revenues) continues to bolster the top and bottom lines.

PCOP: Accelrys' parent Pharmacopeia announced that Daiichi Pharmaceutical Co. Ltd. initiated human trials with a product containing a small molecule identified and optimized by Pharmacopeia and Daiichi scientists. The initiation of these trials triggers a milestone payment to Pharmacopeia. PCOP will be entitled to addi-

tional milestone payments and sales royalties if the collaboration is successful.

NVEC: Highlighted last month, NVEC soared nearly 50% to an all-time high of \$60.33 before profit-taking settled in. While we'd look for a pull-back before buying aggressively again, catalysts in the next few months include MRAM sampling by Cypress [CY] and potential licensing deals.

TINY: Harris & Harris Group shares went on a tear, adding 35%. See "Bush and the Nano Pretenders," on page 3 for more on its valuation.

SKYE: SkyePharma reached an agreement with Novartis [NVS] to jointly develop a new product for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Novartis will make an initial payment to SkyePharma and future development milestone and royalty payments if the co-development project progresses successfully.

FLML: Flamel stock has been battleground in the last month, bouncing 42.5% off its November low of \$23.09 to peak again at \$32.90. At a recent \$24.80, with a hoard of cash and an exciting new technology platform, we believe FLML represents an attractive risk-reward for investors.

*Stock prices as of December 11, 2003

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DNA-assisted dispersion and separation of carbon nanotubes

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Carbon nanotubes are man-made one-dimensional carbon crystals with different diameters and chiralities. Owing to their superb mechanical and electrical properties, many potential applications have been proposed for them. However, polydispersity and poor solubility in both aqueous and non-aqueous solution impose a considerable challenge for their separation and assembly, which is required for many applications. Here we report our finding of DNA-assisted dispersion and separation of carbon nanotubes. Bundled single-walled carbon nanotubes are effectively dispersed in water by their sonication in the presence of single-stranded DNA (ssDNA). Optical absorption and fluorescence spectroscopy and atomic force microscopy measurements provide evidence for individually dispersed carbon nanotubes. Molecular modelling suggests that ssDNA can bind to carbon nanotubes through π -stacking, resulting in helical wrapping to the surface. The binding free energy of ssDNA to carbon nanotubes rivals that of two nanotubes for each other. We also demonstrate that DNA-coated carbon nanotubes can be separated into fractions with different electronic structures by ion-exchange chromatography. This finding links one of the central molecules in biology to a technologically very important nanomaterial, and opens the door to carbon-nanotube-based applications in biotechnology.

DNA is a naturally occurring polymer that plays a central role in biology. Many unique properties of DNA have inspired a search for non-biological applications for it. Molecular recognition between complementary strands of a double-stranded DNA has been used to construct various geometric objects at the nanometre scale¹, and to organise the assembly of colloidal particles^{2,3}. The π -stacking interaction between bases in DNA has prompted the exploration of its electronic properties for possible use in molecular electronics⁴. Less used are the potential inorganic substrate-binding properties of DNA, in contrast to recently demonstrated efficacy of oligopeptides for this purpose^{5,6}. Carbon nanotubes^{7,8} have excellent mechanical and electrical properties that have led to the proposal of many potential applications. Separation and assembly of nanotubes are required for many applications⁹, but their polydispersity and poor solubility in both aqueous and non-aqueous solution make this a big challenge.

A large molecular library can be formed by single-stranded DNA (ssDNA), which offers an intriguing possibility for carbon nanotube binding: depending on its sequence and structure, aromatic nucleotide bases in ssDNA may be exposed to form π -stacking interactions with the side-wall of carbon nanotubes. To search for DNA sequences that bind carbon nanotubes, we followed a well-established *in vitro* evolution procedure¹⁰. We discovered that DNA binding to carbon nanotubes is extremely effective and facile. Specific conditions for dispersion depend on the source of carbon nanotubes. For purified HiPco nanotubes (high-pressure CO reactor process¹¹, Carbon Nanotechnologies), we found that practically any ssDNA would work in the presence of a denaturant, with mild sonication. The primary role of denaturant seems to be to disrupt base-pairing; one can obviate its use by avoiding G(guanine):C(cytosine) and A(adenine):T(thymine) base-pairing interactions in the sequence design. For as-produced HiPco nanotubes, in addition to ssDNA, short double-stranded DNA and total RNA extracted from *Saccharomyces cerevisiae* and *Escherichia coli* can also disperse carbon nanotubes. In this case, however, vigorous sonication is needed for effective dispersion. DNA-coated carbon nanotube (DNA-CNT) solutions are stable for months at room temperature. Removal of free DNA by either anion-exchange column chromatography or nuclease digestion does not cause nanotube flocculation, indicating that DNA binding to carbon nanotubes is very strong. Even though there is no reliable way to determine the percentage of individually dispersed nanotubes in solution, all of our evidence suggests that DNA converts bundled CNT into individual tubes. As is seen in Fig. 1, the electronic absorption spectra of DNA-CNT solutions show well-resolved structures and systematic dependence on pH. We have also observed

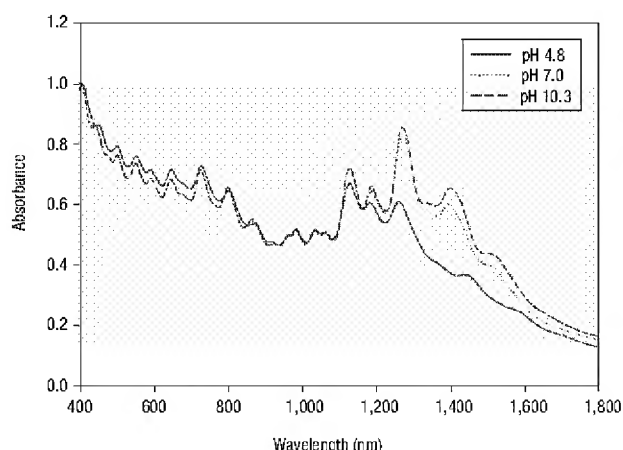


Figure 1 Electronic absorption spectra of DNA-CNT: in 0.05 M sodium acetate/0.1 M sodium chloride (pH 4.8), 0.05 M sodium phosphate/0.1 M sodium chloride (pH 7), and 0.05 M sodium bicarbonate/0.1 M sodium chloride (pH 10.3), respectively. The stock solutions of DNA-CNT were prepared as described in the Methods section, with 1 mg as-produced HiPco carbon nanotube and 1 mg of T30 DNA in 1 ml of corresponding buffer solution. The spectra were taken with two-fold dilution of the stock solutions using the corresponding buffer and 0.1 M sodium chloride solution. The optical path length is 1 mm.

strong near-infrared fluorescence from DNA-CNT solutions. These features are characteristic of individually dispersed nanotube solutions, obtained only recently with surfactants after rather more intense sonication treatment¹². Atomic force microscopy measurements show that DNA-CNTs have a length distribution from 50 to 1,000 nm, with tube diameters ranging from 1 to 2 nm. The diameters are larger than the 0.7 to 1.1 nm expected for HiPco tubes^{11,13}, but are consistent with DNA coating of nanotubes.

To explore the influence of the DNA sequence and length on dispersion efficiency, we tested some simple patterns of sequence with defined lengths. The dispersion efficiency was measured by the optical absorption intensity of the dispersion solution at 730 nm, which is relatively invariant with respect to pH changes. Among fixed length (60-mer) homopolymers that can be made by solid-phase synthesis, we found that poly(T) has the highest dispersion efficiency. Among the four different lengths (60-, 30-, 21- and 15-mer) of poly(T) examined, we found that T30 gave the highest yield.

An ssDNA molecule is quite flexible in bond torsion within the sugar-phosphate backbone. Indeed, we postulate that it is this flexibility that allows the molecule to find low-energy conformations that maximize base-nanotube stacking interactions while exposing the sugar-phosphate groups to water. To obtain putative binding structures, and to quantify approximately the thermodynamics of binding, we simulated interaction between ssDNA molecules and carbon nanotubes. Figure 2 shows the results of this process for poly(T) around a carbon nanotube with (10,0) chiral vector. Although the remaining results presented in the following paragraphs are for this particular case, we note that even within the range of preferred torsion angles we have found, there are many allowed ways in which short ssDNA strands can bind to the nanotube surface. These include helical wrapping with right- and left-handed turns or simply surface adsorption with a linearly extended structure. Figure 2a reveals an overall right-handed helical wrapping of the ssDNA chain around the nanotube. Note that the bases are extended from the backbone and stack onto the nanotube. The sugar-phosphate backbone itself is exposed and would easily be solvated. Figure 2b, an end-on view, shows that the ssDNA chain forms

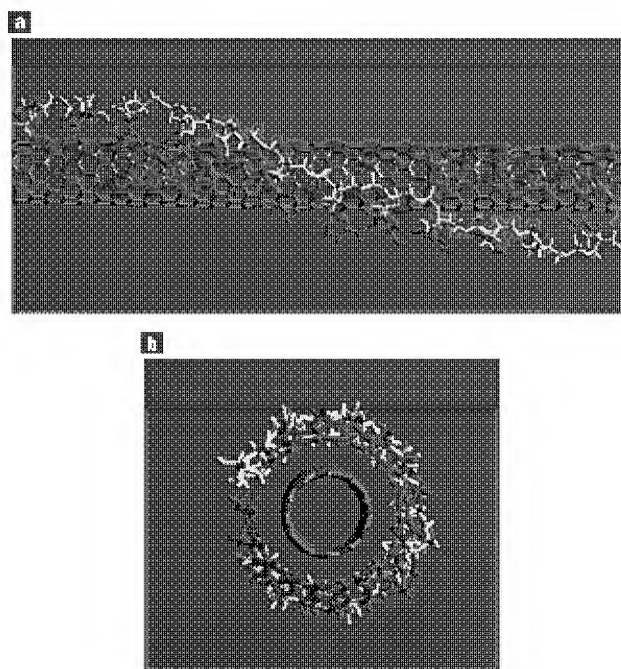


Figure 2 Binding model of a (10,0) carbon nanotube wrapped by a poly(T) sequence. **a**, The right-handed helical structure shown here is one of several binding structures found, including left-handed helices and linearly adsorbed structures. In all cases, the bases (red) orient to stack with the surface of the nanotube, and extend away from the sugar-phosphate backbone (yellow). **b**, The DNA wraps to provide a tube within which the carbon nanotube can reside, hence converting it into a water-soluble object.

a shell encasing the nanotube and providing the hydrophilic sugar-phosphate backbone on the exterior.

To estimate the thermodynamics of binding, we compared the minimized energy of the DNA-CNT hybrid shown in Fig. 2 with that of the individual nanotube and the poly(T) strand (minimized separately). This resulted in a binding enthalpy of about -1.17 eV nm^{-1} . The entropic penalty was estimated by treating each allowed backbone torsion to be equivalent in solution, and by comparing the allowed conformations with the restricted set on the nanotube surface, resulting in about 0.15 eV nm^{-1} at 300 K, indicating that the enthalpy of binding is the dominant term in the free energy of binding. In comparison, poly(A) and poly(C) are known to strongly self-stack in solution¹⁴, therefore they have smaller free energies of binding to carbon nanotubes. This is consistent with our finding that poly(A) and poly(C) have lower dispersion efficiency than poly(T). The free energy of association of two nanotubes, calculated in the same manner, was found to be -1.12 eV nm^{-1} , similar to values reported in the literature^{15,16}. Clearly the binding of ssDNA onto carbon nanotubes can compete quite effectively with the known strong tendency of nanotubes to cling to each other and form ropes. The foregoing calculations do not account for the effect of solvent, but that may well favour the binding even further because the DNA backbone is available to be solvated, hence reducing the surface tension associated with the de-solvated nanotube.

In comparison with other polymers that also disperse carbon nanotubes^{17,18}, DNA seems to be much more efficient. In a typical experiment, 1 mg of DNA can disperse an equal amount of as-produced HiPco CNT in 1 ml volume, yielding 0.2 to 0.4 mg ml^{-1} CNT solution

after removal of non-soluble material by centrifugation. Such a CNT solution can be further concentrated by tenfold to give a soluble CNT concentration as high as 4 mg ml^{-1} . DNA chain flexibility and backbone charge may all contribute to such high dispersion efficiency. In addition, DNA offers the advantage of defined length and sequence, and well-developed chemistries for functionalization. The latter provides a way to functionalize the carbon nanotube surface without modifying it covalently. As a demonstration, we made DNA-CNT using an oligonucleotide that was modified at one end with biotin. We observed biotin-dependent deposition of nanotubes onto streptavidin-coated agarose beads. This demonstration also illustrates a way to control the placement of carbon nanotubes on solid substrate.

Separation of carbon nanotubes according to their electronic properties is a crucial technical challenge for which no solution currently exists. DNA-CNT offers potential solutions to this problem. The phosphate groups on a DNA-CNT hybrid provide a negative charge density on the surface of the carbon nanotube, the distribution of which should be a function of the DNA sequence and electronic property of the tube. Everything else being equal, DNA-metallic CNT is predicted to have less surface charge than DNA-semiconducting CNT due to the opposite image charge created in the metallic tube. To take advantage of such a difference for CNT separation, we explored ion-exchange liquid chromatography. When (C/T)60 (a 60-base long random ssDNA composed of C and T only) dispersed carbon nanotube was injected into a strong anion-exchange column, both free DNA and DNA-coated nanotubes adsorbed on it. The chromatogram (Fig. 3a) shows the elution of two well-separated bands by a NaSCN salt gradient, corresponding to free DNA (first band) and DNA-CNT (second band), respectively. We measured electronic absorption spectra for all the fractions (fraction 46 to 55) in the DNA-CNT band, and found a remarkable difference in early fractions. Figure 3b compares the spectrum for fraction 47 (f47) with that of fraction 49 (f49). Although all the absorption peaks are present in both fractions, they are $\sim 5 \text{ nm}$ blue-shifted in f47. In addition, f47 has more pronounced absorption in the metallic M_{11} ($400\text{--}600 \text{ nm}$) band¹², and weaker absorption in the semiconductor E_{11} band ($900\text{--}1,600 \text{ nm}$) than f49, indicating that the early fraction f47 is enriched with metallic tubes. Raman spectroscopy measurement (with 532 nm excitation) on all fractions showed that f47 has the strongest Breit–Wigner–Fano line-shape component in the tangential G band near $1,600 \text{ cm}^{-1}$, characteristic of metallic tubes¹³. These results are consistent with our prediction that metallic tubes would elute first from the anion exchange column because of their reduced effective charges. Figure 3c provides a direct visual comparison showing the pink colour of f47 as a result of its absorption spectrum.

Length variation in dispersed CNT is an important factor to consider in charge-based separation. Indeed, we observed a gradual increase of average tube length from early to late fractions. Atomic force microscopy measurements showed (Fig. 4a and 4b) that there is a difference in average length of carbon nanotubes for the two fractions ($117 \pm 68 \text{ nm}$ for f47, $208 \pm 146 \text{ nm}$ for f49, Fig. 4c). To exclude the possibility that changes in optical transitions are caused by changes in tube length, we prepared shorter DNA-CNT ($\sim 200 \text{ nm}$ average length) using higher sonication power (8 W) and longer duration (120 min) in the dispersion procedure. As was expected, the same kind of changes in optical transitions was still observed in fractions from the shorter tube preparation. In conclusion, even though our metallic/semiconductor tube separation is convoluted by tube length variations, it is nevertheless the first demonstration of CNT separation by electronic properties, illustrating another important utility of DNA–CNT hybrid.

In summary, we have discovered that nucleic acid polymers form a hybrid material with carbon nanotubes. This finding links one of the central molecules in biology to a technologically very important nanomaterial, and opens the door to carbon-nanotube-based applications in biotechnology. The unique attributes of this material provide many ways to manipulate carbon nanotubes in aqueous

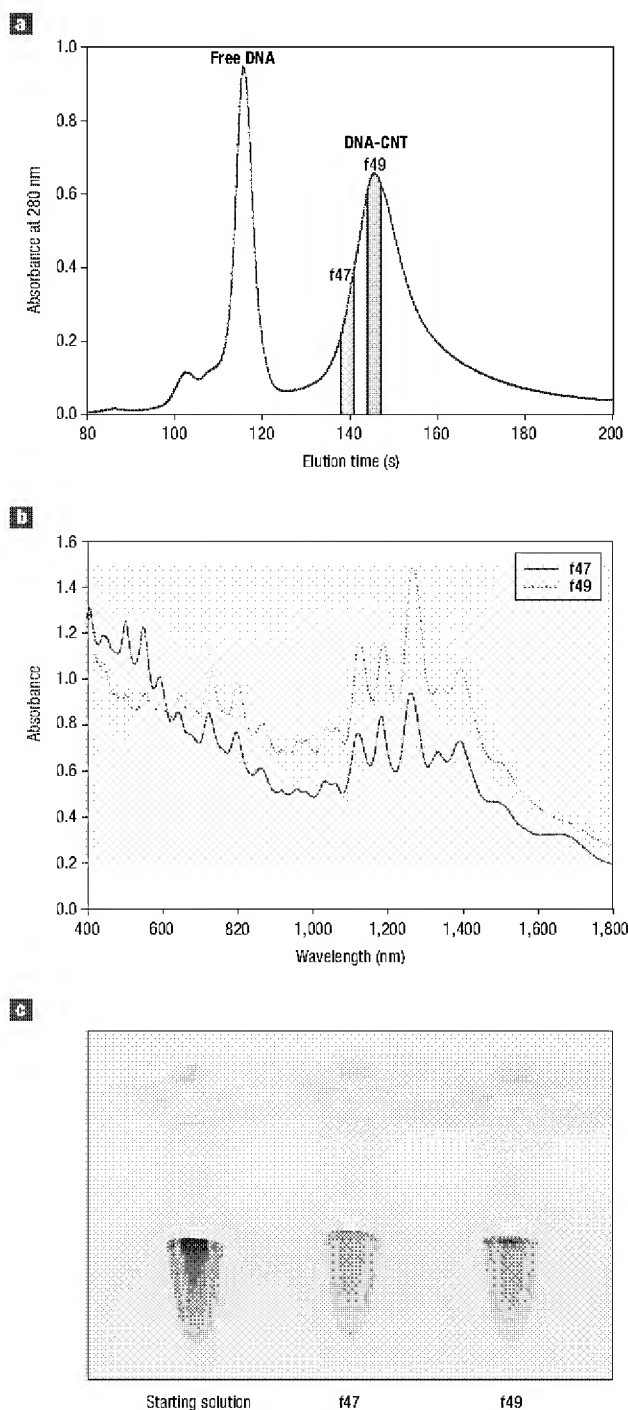


Figure 3 Separation of DNA-CNT by anion exchange chromatography.

a, Chromatogram of anion-exchange column separation of (C/T)60 dispersed carbon nanotubes, showing the two different bands due to free DNA and DNA-CNT. The position of fractions 47 (f47) and 49 (f49) are shown. **b**, Electronic absorption spectra of two fractions f47 and f49. Before the measurement, fractions were centrifuged using a microcon spin filter YM100 (Millipore), and re-suspended in 0.1 M sodium chloride D_2O solution with an appropriate volume to concentrate f47 by fivefold, and f49 by 1.67-fold. **c**, Visual comparison of DNA-CNT solutions of the starting material, f47 and f49.

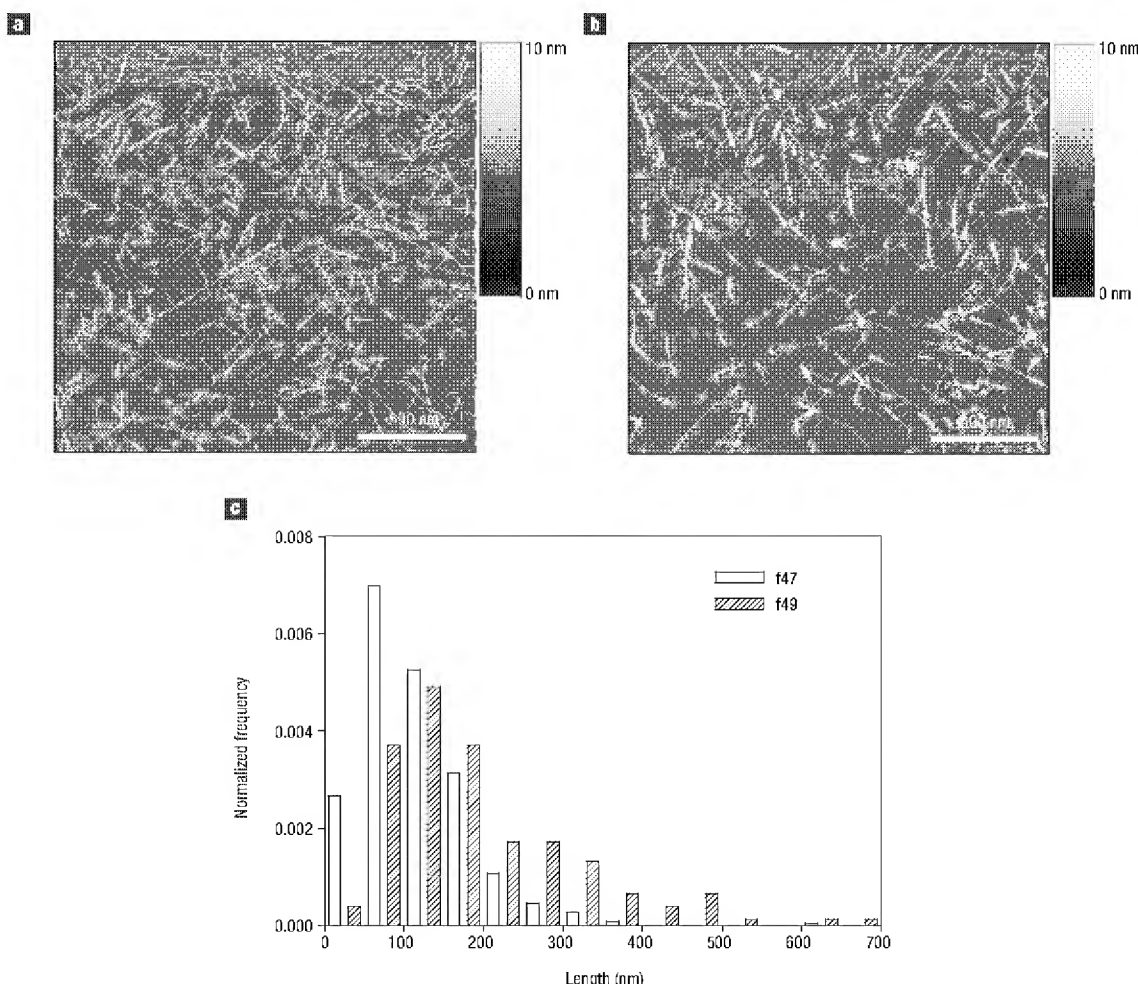


Figure 4 Analysis of DNA-CNT fractions by atomic force microscopy (AFM). **a**, AFM image of DNA-CNT from f47. **b**, AFM image of DNA-CNT from f49. **c**, Histogram of DNA-CNT length variation (f47: 117 ± 68 nm, f49: 208 ± 146 nm).

solutions, including separation and surface modification. The potential of differential binding by DNA or RNA to carbon nanotubes of different diameter and chirality remains to be explored.

METHODS

DNA DISPERSION OF CARBON NANOTUBES

In a typical dispersion experiment, 1 mg of as-produced HiPco nanotube (Carbon Nanotechnologies) was suspended in 1 ml aqueous DNA (Integrated DNA Technologies) solution (1 mg ml⁻¹ ssDNA, 0.1 M NaCl, and in some experiments an appropriate pH buffer). The mixture was kept in an ice-water bath and sonicated (Sonics, VC130 PB) for 90 min at a power level of 3 W. After sonication, the samples were divided into 0.1 ml aliquots, and centrifuged (Eppendorf 5415C) for 90 min at 16,000g to remove insoluble material, leaving DNA-dispersed nanotube solutions at a mass concentration in the range of 0.2 to 0.4 mg ml⁻¹.

COMPUTER MODELLING

Computations were conducted using a consistent force field (pcff) and a commercial molecular modelling program (Discover in Cerius² v 4.7, Accelrys, San Diego). Starting from a single nucleotide, ssDNA molecules were constructed by the sequential addition of nucleotide residues to the existing ssDNA molecule in the vicinity of the carbon nanotube surface. Following each addition, the structure was minimized to energy convergence. Because of the plurality of local minima in conformational degrees of freedom, this procedure would normally yield a variety of ssDNA structures. However, by repeatedly starting the minimization using the torsion angles described below, we found a set of conformations that allowed each base to stack onto the folded graphene surface, and the entire chain to bind to the nanotube in a helical wrapping or linear adsorption fashion.

Initial torsion angles chosen corresponded to those that would sequentially bring the base of the added nucleotide at the distance and orientation preferred for stacking interaction. Following minimization, torsion angles (see ref. 14 for definition) were found to belong to one of two sets, either

(a) ($\chi, \alpha, \beta, \gamma, \delta, \epsilon, \zeta$) = ($-138 \pm 7, 168 \pm 13, 152 \pm 11, 57 \pm 7, 99 \pm 9, 57 \pm 20, 128 \pm 18$),

or

(b) ($\chi, \alpha, \beta, \gamma, \delta, \epsilon, \zeta$) = ($180 \pm 6, 168 \pm 13, 84 \pm 11, 162 \pm 7, 99 \pm 9, 113 \pm 4, 73 \pm 8$).

It seems that our proposed CNT-constrained binding structure restricts conformations to these two correlated sets. These are consistent with known allowed ranges, but are quite different from those for double-stranded B-DNA¹⁴. The principal difference is that in B-DNA, the backbone torsion result in the normal to the plane of the base orienting along the helical axis. By contrast, in the nanotube-binding structure, the normal to the base orients perpendicular to the helical and nanotube axes.

AFM

The sample solution was deposited onto a piece of mica pre-treated with 1 M MgSO₄ solution to enhance DNA adsorption, and rinsed with water and dried before measurement. Tapping mode was used to acquire the images under ambient conditions (Digital Instruments Dimension 3100).

ION-EXCHANGE COLUMN SEPARATION

A strong anion-exchange column HQ20 (Applied Biosystems) was chosen because it is packed with resins that are functionalized by quaternized polyethyleneimine, which is expected to bind to the negatively charged phosphate groups of DNA. To increase sample recovery, the top filter of the column was removed. In a typical experiment, a volume of 800 μ l of DNA-dispersed carbon nanotubes at a concentration of ~ 100 μ g ml⁻¹ was injected into the column (4.6 mm by 100 mm, 1.8 ml bed volume) mounted on a BioCAD/SPRINT HPLC system (Applied Biosystems), and eluted with a linear salt gradient (0 to 1.8 M NaSCN in 20 mM MES buffer at pH 7) in 40 ml volume at a flow rate of 10 ml min⁻¹. Fractions were collected in 0.5 ml aliquots.

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Competing financial interests

The authors declare that they have no competing financial interests.